Randomized Trial of Human Milk Cream as a Supplement to Standard Fortification of an Exclusive Human Milk-Based Diet in Infants 750-1250 g Birth Weight

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Objective To evaluate whether premature infants who received an exclusive human milk (HM)-based diet and a HM-derived cream supplement (cream) would have weight gain (g/kg/d) at least as good as infants receiving a standard feeding regimen (control).

Study design In a prospective noninferiority, randomized, unmasked study, infants with a birth weight 750-1250 g were randomly assigned to the control or cream group. The control group received mother's own milk or donor HM with donor HM-derived fortifier. The cream group received a HM-derived cream supplement if the energy density of the HM tested <20 kcal/oz using a near infrared HM analyzer. Infants were continued on the protocol until 36 weeks postmenstrual age. Primary outcomes included growth velocities and amount of donor HM-derived fortifier used. The hypothesis of noninferiority was established if the lower bound of the one-sided 95% CI for the difference in weight velocities exceeded −3 g/kg/day.

Results There were no differences between groups in baseline demographics for the 78 infants studied except racial distribution (P = .02). The cream group (n = 39) had superior weight (14.0 ± 2.5 vs 12.4 ± 3.0 g/kg/d, P = .03) and length (1.03 ± 0.33 vs 0.83 ± 0.41 cm/wk, P = .02) velocity compared with the control group (n = 39). There were no significant differences in amount of fortifier used between study groups. The 1-sided 95% lower bound of the CI for the difference in mean velocity (cream-control) was 0.38 g/kg/d.

Conclusions Premature infants who received HM-derived cream to fortified HM had improved weight and length velocity compared with the control group. HM-derived cream should be considered an adjunctive supplement to an exclusive HM-based diet to improve growth rates in premature infants. *(J Pediatr 2014;165:915-20)*.

Human milk (HM) feeding is associated with substantial benefits to the health and development of infants, especially premature infants.[1] The American Academy of Pediatrics recommends that all preterm infants receive HM including donor HM if mother's own milk is unavailable.[2] Recently, the use of an exclusive HM-based diet for very low birth weight (BW) infants has significantly risen. Sullivan et al found that an exclusive HM-based diet in infants ≤1250 g BW reduced the rate of necrotizing enterocolitis (NEC) by 50% and surgical NEC by 90%[3] In this same study, there was no difference in growth between infants receiving an exclusive HM-based diet compared with infants receiving bovine milk fortifier.[3]

A large cohort study of infants <1000 g BW showed that growth velocities greater than current guidelines of 15 g/kg/d are needed to ensure that infants maintain their BW percentile on the growth curve and avoid extrauterine growth restriction.[4] One study evaluating macronutrient composition of mother's milk and donor HM found high variability in fat, protein, and energy content.[5] Another study evaluating the energy content of donor HM found that on average, donor milk was 19 kcal/oz but 25% of the samples had caloric values <17.3 kcal/oz, which is significantly lower than the 20 kcal/oz or more reported in mother's milk.[6]

A novel pasteurized donor HM-derived cream supplement is now available. It can be added to an infant's diet to help improve overall caloric intake without substantially altering the total feeding volume given to the infant. We hypothesized that premature infants who received an exclusive HM-based diet and a HM-derived cream supplement (cream) would have weight gain (g/kg/d) at least as good as infants receiving a standard feeding regimen (control).

BW	Birth weight
HC	Head circumference
HM	Human milk
NEC	Necrotizing enterocolitis
PMA	Postmenstrual age

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Funded by the US Department of Agriculture (USDA)/ Agricultural Research Service (ARS) (58-6250-6-001) and National Center for Research Resources General Clinical Research for Children (RR00188). Prolacta Bioscience provided the product for the study and assisted in data analysis. Contents of this publication do not necessarily reflect the views or policies of the USDA, nor does mention of trade names, commercial products, or organizations imply endorsement by the US government. A.H. and C.B. received financial support and receive speaker honoraria from Prolacta Bioscience. M.L. and D.R. are employees of Prolacta Bioscience. The other authors declare no conflicts of interest.

Registered with ClinicalTrials.gov: NCT01487928.

http://dx.doi.org/10.1016/j.jpeds.2014.07.005

Methods

Using a prospective randomized study design, preterm infants 750 to 1250 g BW receiving an exclusive HM-based diet were identified after admission to the Neonatal Intensive Care Unit of the 2 study centers, Texas Children's Hospital (Houston, Texas) or University Health System at San Antonio (San Antonio, Texas). Inclusion criteria were 750-1250 g BW, reasonable expectation of survival for study duration through 36 weeks postmenstrual age (PMA) or weaned from fortification (whichever comes first), adherence to a feeding protocol providing an exclusive HM-based diet and potentially a donor HM-derived cream supplement, achievement of enteral feeds by 21 days of life, and informed consent from parent or legal guardian. Infants were excluded that had major congenital anomalies or clinically significant congenital heart disease, low expectation for survival, high potential for early transfer to a nonstudy institution, enrollment in another clinical study that affected nutritional management, failure to start minimum enteral feeds before 21 days of life, presence of intestinal perforation or stage 2 NEC by modified Bell Criteria[7] prior to tolerating fortified feeds, or inability to participate in the study for any reason based on the decision of the study investigator.

This study was approved by the Institutional Review Board of Baylor College of Medicine and Affiliated Hospitals and The University of Texas Health Science Center at San Antonio. Infants meeting inclusion criteria were identified, and their parents approached for consent until 21 days of age as infants needed to have started enteral feeds by this time and prior to initiation of fortification. After informed written parental consent was obtained, infants were randomized into 1 of 2 groups via blocks of 4, the size of which was blinded (cream or control group). Because of the nature of the interventions by which the nutrition was prepared and delivered, masking of the study groups was not possible at 1 site. The cream supplement mixes readily with HM and its addition does not change the composition or consistency of the HM. At 1 site, we were unable to prepare the milk and deliver it to the infant in a blinded fashion for logistical reasons.

The sample size was determined based on the primary endpoint of the rate of weight gain from initiation of enteral feeds to 36 weeks PMA. Based on available data evaluating an exclusive HM-based diet, the SD of weight gain was 4 g/kg/d.[3] For this determination, we hypothesized that we would identify a lack of inferiority (defined as a difference of weight gain of less than 3 g/kg/day, ie, a lower bound of −3) in the mean weight gain for the cream group compared with the control group. With a 1-sided 5% significance level and 90% power, a sample size of 62 (n = 31 per group) was needed to demonstrate a difference of this magnitude between the 2 study groups. However, it was anticipated that some infants might not require cream supplement in the intervention group because their HM was ≥20 kcal/oz. To account for this, the sample size was increased by 25% to 78 (n = 39 per group). The cream group was defined as the intent to treat group although some infants in this group might not have received cream supplement.

Infants were fed an exclusive HM-based diet according to the investigative site's standard of care. Infants received mother's own milk supplemented with pasteurized donor HM when mother's milk was unavailable. Donor HM was from 2 sources (Texas Children's Hospital received donor HM from Prolacta Bioscience, Industry, California and University Health System at San Antonio received donor HM from a member milk bank of the Human Milk Banking Association of North America). Both study sites followed protocols and standards specific to milk collection, transportation, storage, preparation, and fortification. The standard feeding regimen provided each group HM fortified with pasteurized donor HM-derived fortifier, Prolact+H^2MF (Prolacta Bioscience, Industry, California[8]). Fortification began by the time infants were tolerating 100 mL/kg/d of enteral feeds if not sooner. Once fortified feeds were tolerated, the caloric content of HM was determined daily from a 24-hour batch sample using a commercially available near infrared milk analyzer (Spectrastar 2400RTW; Unity Scientific, Brookfield, Connecticut). This caloric information was only available to study investigators and was not part of routine care at either study site. For the control group, infants received the standard feeding regimen (without cream supplement) and caloric information was recorded for study purposes. The cream group received the same standard feeding regimen with the addition of a donor HM-derived cream supplement if the HM they were receiving was found to be <20 kcal/oz after analysis. The donor HM-derived cream supplement, Prolact CR, (Prolacta Bioscience[8]) is standardized to 25% lipids and contains 2.5 kcal/mL. The appropriate amount of cream was added to HM to bring the caloric content to approximately 20 kcal/oz. Donor HM or own mother's milk was adjusted with cream supplement to a target level of 20 kcal/oz because it is generally assumed that mother's milk is 20 kcal/oz. The control group received fortification based on the assumption that the HM was 20 kcal/oz.

Infants were followed for study duration from initiation of enteral feeds until 36 weeks PMA or weaned from fortifier (whichever occurred first), transferred to a nonstudy institution, removed from the study, or death. Weight was recorded daily. Recumbent length and head circumference (HC) were measured weekly using a length board and tape measure, respectively. Primary outcomes included growth velocity (weight, length, and HC) and the amount of donor HM-derived fortifier used. The incidence of sepsis, NEC, or death was recorded. Weight gain velocity (g/kg/d) was calculated using the Patel Method.[9]

All quantitative data, including the growth variables and volumes of nutrition, were summarized by the use of descriptive statistics (mean ± SD and median ± IQR). Qualitative data were summarized using proportions and percentages. The primary analytical approach to the study endpoint of the rate of change in body weight from initiation of enteral

feeding to 36 weeks PMA or weaned from fortifier employed an intent-to-treat paradigm. The intent-to-treat population for this study was defined as all randomized subjects who received any enteral nutrition. If a study subject failed to complete the requisite study period (through 36 weeks PMA or weaned from fortifier), then the rate of change in weight was calculated for the time on study. The comparison between the study arms with respect to the primary endpoint was made by the use of a 1-sided 95% CI for the difference in rate of weight change over the study period. Groups were compared using the 2-sample t test, χ^2 test, and Fisher exact test. Statistical significance was defined as $P < .05$. Statistical analyses were performed using NCSS 9 software-2013 (NCSS, LLC, Kaysville, Utah).

Results

We enrolled 78 infants (Figure). There were no significant differences in infant demographics and characteristics at the time of study enrollment except racial distribution (Table I). For study duration, infants in the cream group had greater weight and length velocity as well as greater weight and length velocity from the time they regained BW compared with the control group (Table II). There was no significant difference in HC growth (Table II). The 1-sided 95% lower bound of the CI for the difference in mean velocity (cream-control) was 0.38 g/kg/d, which was above the value of −3 determined as the lower bound for lack of inferiority. There were no significant differences in the amount of fortifier used between the groups. There were no cases of NEC and no deaths among study infants in either group (Table III). The number of sepsis episodes were not significantly different between the 2 groups (Table III). None of the infants in the cream group had the intervention discontinued because of intolerance or other adverse outcomes. 33 of the 39 infants (85%) that were assigned to the cream group received the cream supplement including all 11 infants assigned to the cream group at the San Antonio study site. The mean (±SD) daily amount of cream supplement given to infants requiring cream was 5.1 ± 2.4 mL (median = 4.8 mL). The amount of cream supplement given to infants requiring cream varied day to day as the 24-hour batch of HM was sampled for caloric analysis each day.

Caloric content (kcal/oz) of mother's own milk (21.2 ± 5.6 vs 18.8 ± 5.6, $P < .01$) and donor HM (21.8 ± 1.5 vs 20.2 ± 2.1, $P < .01$) differed between study sites with higher caloric content at Texas Children's Hospital. We found a

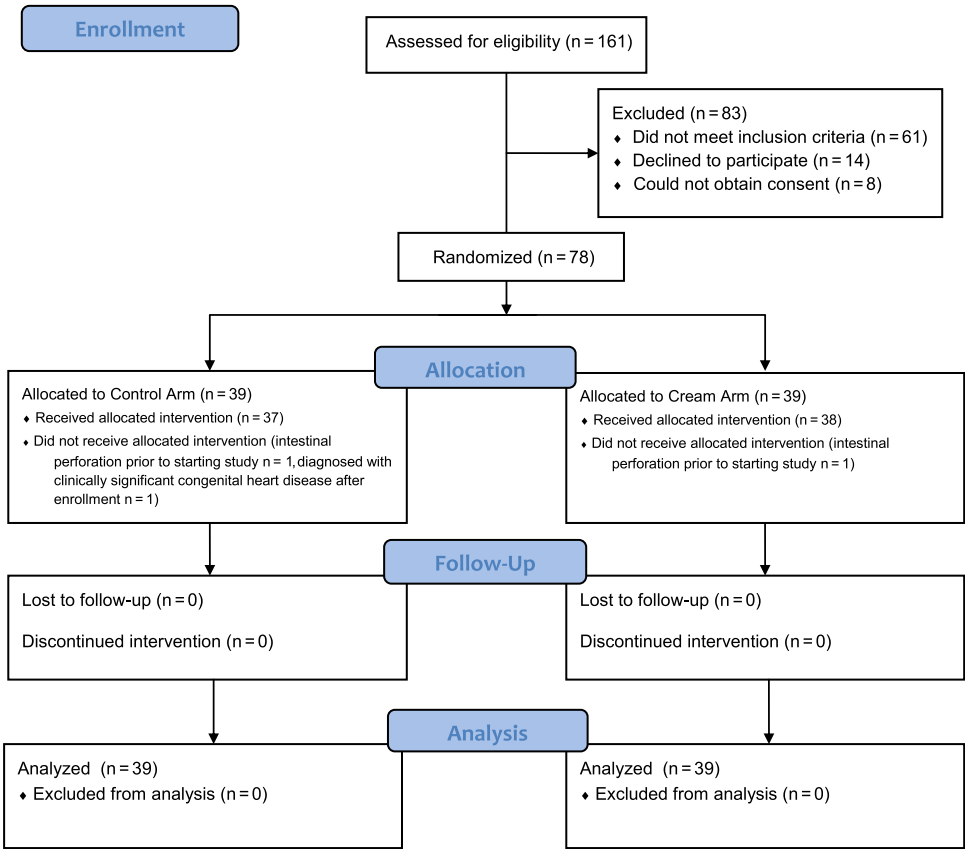

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Figure. CONSORT diagram.

Table I. Infant demographics and characteristics

	Control group, n = 39	Cream group, n = 39	*P* value
BW, g	972 ± 150*	969 ± 140	.92
Gestational age, wk	27.7 ± 2.1	27.6 ± 1.6	.88
Sex, % male	54	49	.65
Race, %, Hispanic/White/Black/other	51, 23, 21, 5	20, 26, 46, 8	.02
Apgar at 5 min	7 ± 2†	7 ± 4†	.43
Mechanical ventilation, %	21	18	.77
Antenatal steroids, %	80	80	1.0

*Mean ± SD.
†Median (IQR).

1.2 kcal/oz difference in caloric content when comparing the milk analyzer results with primary AOAC International laboratory methods. Adjusting the caloric content of the milk to reflect the true kcal/oz gives the caloric content of mother's own milk at each center (20 vs 17.6 kcal/oz) and donor HM (20.6 vs 19 kcal/oz), respectively.

Discussion

We found that adding a unique HM-derived cream product significantly enhanced the growth of very preterm infants. This study evaluated an entirely HM-based approach to nutrition in this group of infants that includes the use of a human derived fat supplement.

HM feeding, appropriately fortified, is the recommended nutritional source for all preterm infants.[2] Studies have shown than an exclusive HM-based diet decreases the incidence of NEC and parenteral nutrition days.[3,10] A pasteurized donor HM-derived cream supplement is a source of fat calories to increase the caloric density of a HM-based diet without a substantial increase in the volume of feeds or using non-HM based nutritional products. Recent studies have reported that the caloric content of mother's milk and donor HM is often <20 kcal/oz, and fat content is the most variable component.[5,6,11] In this study, for infants in the intervention group, if the caloric content of the milk they were receiving was <20 kcal/oz, then donor HM-derived cream supplement was added to increase the calories to 20 kcal/oz. Infants received the supplement starting at 100 mL/kg/d of fortified feeds while they were advancing to full enteral volume. It has become evident from recent reports that early nutrition improves growth, decreases postnatal growth failure, and improves outcomes.[12-14] Appropriate growth of preterm infants is crucial to improved outcomes. For example, Ehrenkranz et al reported that as the rate of weight gain and HC increased in extremely low BW infants, the incidence of cerebral palsy and poor neurodevelopmental scores decreased significantly at 18-22 months' corrected age.[14]

Very low BW infants may benefit from individualized fortification of their enteral nutrition because of the variability of the macronutrient composition of HM.[5] The donor HM-derived fortifier provides and often exceeds (depending on the amount given) the recommended amounts of protein (g/kg/d) for premature infants.[15,16] As fat concentration varies between HM samples and may be low in some cases, infants may benefit from extra fat in addition to fortifiers. However, published data are limited in this regard. A Cochrane review evaluated fat supplementation of HM for promoting growth in preterm infants and found that there was insufficient evidence to make recommendations for practice.[17] Polberger and others conducted a double-blind randomized study of 28 infants fed HM fortified with HM protein and/or HM fat.[18] For the 14 infants that received HM fat, there was no difference in short term growth.[18] HM was analyzed for macronutrient composition in this study but there was not a description of the amount or the method of how HM fat was supplemented to the feeds.

Results from our study show that infants who received HM fat had improved short-term growth in weight and length. Although we did not perform body composition studies on these infants, the increase in length velocity in addition to weight gain suggests that infants had gains in lean body mass.[15] Preterm infants require a high protein to energy ratio to achieve catch up growth without fat accretion and that growth should focus on length gain and lean body mass.[15] Infants only received donor HM-derived cream supplement when the HM calories were <20 kcal/oz to raise the calories to 20 kcal/oz, which is the caloric content reported for mature HM.[15,16]

Other strategies aimed at increasing the amount of fat calories in enteral nutrition include adding medium-chain triglycerides because of potential for high absorption by premature infants. Although this has been used in clinical practice, there is only 1 small study evaluating this supplementation approach. That study did not show an effect on growth when medium-chain triglycerides were added to

Table II. Comparison of growth velocities

	Control group, n = 39	Cream group, n = 39	*P* value
Weight velocity (g/kg/d)	12.4 ± 3.9*	14.0 ± 2.5	.03
Length velocity (cm/wk)	0.83 ± 0.41	1.03 ± 0.33	.02
HC (cm/wk)	0.84 ± 0.22	0.90 ± 0.19	.21
Weight velocity from time infant regained BW (g/d)	18.6 ± 6.4	21.8 ± 5.4	.02
Weight velocity from time infant regained BW (g/kg/d)	13.7 ± 4.0	15.7 ± 2.5	.02
Length velocity from birth (cm/wk)	0.76 ± 0.29	0.95 ± 0.34	.01
HC from birth (cm/wk)	0.62 ± 0.21	0.64 ± 0.19	.58

*Mean ± SD.

Table III. Clinical outcomes of study infants

	Control group, n = 39	Cream group, n = 39	*P* value
NEC (%)	0	0	-
Sepsis (%)	7.7	10.3	1.0
Death (%)	0	0	-

HM.[19] In addition, there are concerns that premature infants have feeding intolerance associated with the addition of oils to HM feeds and that medium-chain triglycerides as used in this setting are not a sterile product. A benefit of the donor HM-derived cream supplement is that it is made from pasteurized donor HM and mixes readily and fully with HM. The addition of HM cream was well tolerated by the infants in this study. We selected infants with a BW between 750 and 1250 g as this population is less likely to have feeding intolerance frequently observed in infants with a BW <750 g. Further studies would be needed in infants <750 g BW to evaluate its use in that group of infants.

A limitation of this study was that the near-infrared milk analyzer used was a secondary method for the measurement of HM and after comparison with primary AOAC methods, despite calibration to bias samples, we found that there was a 1.2 kcal/oz overestimation of the caloric content of the HM samples. Although there is some variation with any method used, the benefit of the milk analyzer used in this study is that it requires a small volume sample and provides results quickly, which is ideal in a clinical setting. There were 2 sources of donor HM used in the study and after correcting for the overestimation, donor HM was higher in mean calories (20.6 $\pm$ 1.5 kcal/oz) at Texas Children's Hospital compared with 19.0 $\pm$ 2.1 kcal/oz at the other site.

The reason for the discrepancy in caloric content between the milk supplied by the 2 banks is 2-fold. Wojcik et al reported that the average caloric value of milk received from a nationwide sample of donors to a commercial milk bank was 19.2 kcal/oz.[6] This corresponds to the caloric content of the donor HM from 1 of the milk banks. The other milk bank (Prolacta Bioscience) formulates its donor HM through the use of very large donor pools and specific processing steps to ensure it contains a minimum of 20 kcal/oz as determined by AOAC primary methodologies. These practices are not currently implemented by any other North American milk bank.

Donor HM has been reported to be lower in protein, fat, and caloric content than mother's own milk and differ from the values reported in the literature for mature HM.[5,6] However, mother's milk and donor HM were similar in mean calories and measured above 20 kcal/oz at Texas Children's Hospital. Therefore, more infants may have qualified for cream supplementation than received it because of the overestimation of calories and the high caloric content of mother's milk and donor HM used in the study. Despite this, infants in the cream group had better weight and length gain compared with the control group.

In conclusion, premature infants who received HM-derived cream supplement to an exclusive HM-based diet had superior weight and length velocity compared with infants who did not receive the supplement. As poor postnatal growth remains a major challenge in neonatology, HM-derived cream supplement should be considered in infants with slow growth or evidence that the HM they are receiving is low in fat content. ■

We would like to thank the following people for their invaluable assistance with the project: Pam Gordon, BSN, RN, RNC-NIC, Cindy Bryant, BSN, CCRN-Neo, Geneva Shores, BSN, RN, RNC-LRN, Nancy Hurst, PhD, RN, IBCLC, Kristina Tucker, BSN, RN, IBCLC, Laurel Laviolette, Mimi Hernandez (all from Texas Children's Hospital, Houston), Texas Children's Hospital Milk Bank Technicians, Neonatal Intensive Care Unit Nurses and Neonatologists at Texas Children's Hospital, Margarita Vasquez MD, Laurie Weaver RNC, Robin Tragus RN, Rachel Jacob RD, (all from University of Texas Health Science Center, San Antonio) NICU Nurses and Neonatologists at University Hospital in San Antonio.

Submitted for publication Apr 14, 2014; last revision received May 28, 2014; accepted Jul 1, 2014.

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Congenital Heart Disease in the Neonatal Period

Mehrizi A, Hirsch MS, Taussig HB. J Pediatr 1964;65:721-6

This study reviewed autopsy records from The Johns Hopkins Hospital from 1927-1959. The analysis was restricted to infants who died within 30 days after birth from a congenital heart defect. A total of 170 autopsies were described.

The 4 most frequent cardiac malformations encountered were ventricle septal defects (18%), transposition of the great vessels (16%), coarctation of the aorta (14.8%), and mitral and/or aortic atresia (11.5%). The next most frequent malformations were patent ductus arteriosus, pulmonary stenosis or atresia with intact ventricular septum, tetralogy of Fallot, truncus arteriosus, the origin of both great vessels from the right ventricle, and cor triloculare. These 10 lesions were found in 151 (88% percent) of the 170 cases.

Most infants with a ventricular septal defect died from prematurity, infection, or a serious associated noncardiac malformation leading the authors to suggest that the development of better care for premature infants would allow these infants to survive the neonatal period. As these improvements evolved, these infants survived early on but they still faced congestive heart failure or pulmonary hypertension in infancy.

Infants with transposition of the great vessels usually died within the first 7 days of life, and their cardiac issue was the primary cause of death. Unlike the other major defects, infants with a coarctation of the aorta lived several days until the patent ductus closed. The majority of these infants had no other malformations. The infants with atresia of either the aortic or mitral valve died within a few days of life, and most had no other issues.

Medical and surgical treatments were not effective for most of neonates described in this paper. Dr Helen Taussig, a coauthor of this article, would be a key developer of the Blalock-Taussig shunt. This revolutionary palliative procedure prolonged the lives of many patients with severe congenital heart defects as they awaited corrective surgery. Prostaglandin E1 would not be available for several more years. The advances in congenital heart surgery were just being developed but would not be available for several years after this study was published. The neonatal mortality rate for the lesions mentioned in this study is close to 0 in 2014 thanks to these and many more advances in the medical and surgical management of these neonates.

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http://dx.doi.org/10.1016/j.jpeds.2014.04.054